

**REMARKS**

Claim 1 and Claims 22-44 are pending. The Applicants thank Examiner Tran for indicating that the subject matter of Claims 7 and 14-16 would be allowable. The limitations of Claim 7 have now been incorporated into independent Claim 1. Claim 1 and the new claims have been revised for clarity. For continuity within the claims, new Claims 22-44 are presented. These claims generally track the prior claims as indicated below, but some additional dependent claims have been added.

**SUPPORT FOR THE AMENDMENT**

The amendments to Claim 1 find support in original Claims 1 and 7. The limitation 10:1 to >1:1 finds support in Claim 7 and in the specification at page 7, line 21. New Claims 22-43 find support as follows: Claims 22-25 (Claim 8, page 7 last two lines-page 8), Claims 26-28 (section [0009] on page 2), Claims 29-31 (Claim 7, section [0024] on page 6), Claims 32-35 (Claims 2-5), Claim 36 (section [0023] on page 6), Claim 37 (Claim 6), Claim 38 (Claim 9), Claim 39-41 (Claims 10-12), and Claim 42-44 (Claim 13, section [0028] on page 8). Accordingly, the Applicants do not believe that any new matter has been introduced.

**REQUEST FOR RECONSIDERATION**

The Applicants respectfully submit that claims depending from Claim 1 should be allowable, in view of the incorporation of the limitations of allowable Claim 7 into Claim 1 and in view of the newly present claims.

The Applicants thank Examiner Tran for the courteous and helpful interview of October 12, 2004. It was suggested that the incorporation of the limitations of Claim 7 into Claim 1 would likely overcome the rejection of Claim 1 and claims depending from Claim 1. It was suggested that Claims 9-12 might be cancelled to facilitate allowance of the

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application. As suggested, the Applicants have now incorporated the limitations of Claim 7 into Claim 1 and reorganized the claim set for continuity and clarity. The subject matter of Claim 9 (“obtainable”) has been merged into Claim 38 which uses the preferred term “obtained by”. Claims 39-41 which correspond to Claims 10-12 have been retained, but they present language that the Applicants believe clarify the inventive concept and further distinguish the crosslinker of these claims from the mixture of crosslinkers in the cited prior art. Favorable consideration and allowance of this application is now respectfully requested.

Restriction/Election

The Applicants thank Examiner Tran for indicating that the Restriction Requirement has been withdrawn.

Claim Objections

Claim 9 was objected to for use of the word “obtainable” instead of the preferred “obtained by”. This objection is moot in view of the cancellation of Claim 9. New Claim 38 uses the term “obtained by”.

Rejection—35 U.S.C. §112, second paragraph

Claims 10-12 and 17 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the cancellation of those claims. New Claims 39-41 are also directed to products which are crosslinking agents. Claim 39 corresponds to prior Claim 10, but its language has been revised in view of page 3, section [0013] of the specification and provides additional description of the claimed crosslinker. Accordingly, the Applicants respectfully submit that this rejection would not apply to the new claims.

Rejection—35 U.S.C. §102

Claims 1-6, 8-12 and 17-21 were rejected under 35 U.S.C. 102(e) as being anticipated by Margolin et al., U.S. Patent No. 6,359,118. This rejection is moot for claims depending from Claim 1, because Claim 1 now incorporates the limitations of Claim 7.

New Claims 39-44 do not depend from Claim 1. However, the Applicants submit that Margolin does not anticipate these claims, because it does not disclose with sufficient specificity the crosslinker of Claim 39. The crosslinking mixture of Margolin is a combination of glutaraldehyde and a diaminoalkane (diaminoocatane), see col. 25, lines 67-col. 26, line 3. Here Margolin et al. disclose the use of a first (diaminooctane) and a second (glutaraldehyde) compound, as defined in the present invention, to treat the crosslinked enzyme crystals (i.e., already crosslinked by the aminoctane to one another) in order to alter the dissolution thereof (column 25, lines 60-66). Indeed, in the passage relied on by the Examiner, i.e., sentence bridging columns 25 and 26, numerous crosslinking agents can be used for the said second crosslinking agent such as glutaraldehyde or glutaraldehyde combined with Tris, lysine, or diaminoctane. Since both Tris buffer and lysine contain a single primary amino group, neither would fall under the definition of the first compound according to the present invention.

Margolin et al describes the crosslinking of glycoprotein crystals through one or more carbohydrates moieties with, for example, diaminoctane. Thus, Margolin et al obtains glycoprotein crosslinked enzyme crystals (CLEC's) closely linked to one another, but not the CLEAs of the present invention. In contrast therewith, the present invention relates to a different crosslinking reaction wherein, as described above, a crosslinker is designed such that a required (functional) distance between the proteins can be obtained. This is not disclosed in Margolin et al.

Margolin et al neither discloses nor suggests a crosslinker obtained by reacting a diamine crosslinking reagent with a compound having at least two aldehyde groups to provide a less tight spatial conformation than crosslinking with a short molecule such as glutaraldehyde (see the specification, page 4, lines 1-6). Indeed, such a technique would appear to frustrate the disclosed goals of Margolin et al. which involve stabilizing the crystalline structure of glycoprotein crystals by crosslinking.

According to Margolin et al, both glutaraldehyde and diaminoctane are added in sequence to the already crosslinked substrate (column 27, lines 27-31). Thus, in Margolin et al, a crosslinker as required by the present invention is not prepared; on the contrary, the glutaraldehyde and diaminoctane are allowed to react with the protein crystals instead of reacting with one another to form a crosslinking agent according to the present invention. Therefore, a crosslinking agent according to the present invention is neither disclosed nor suggested by Margolin et al.

The Applicants respectfully request that this ground of rejection be withdrawn in view of (1) the incorporation of the limitations of allowable Claim 7 into Claim 1 and in view of the arguments above.

**CONCLUSION**

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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